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Defining Subphenotypes for Oral Clefts Based on Dental Development

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Abstract

Individuals with clefts present considerably more dental anomalies than do individuals without clefts. We used dental development to subphenotype clefts with the goal of identifying cleft subgroups that could have specific genetic contributions. We examined 1000 individuals, 500 with clefts and 500 without. We used several clinical features, such as cleft completeness or incompleteness, laterality, and the presence of dental anomalies to assess each individual's cleft status. We performed chi-square and Fisher's exact tests to compare the frequencies of observed anomalies between individuals with and individuals without clefts, and among individuals with different cleft subphenotypes. Agenesis of the lateral incisor on the non-cleft side was the most remarkable observation, and may suggest that such cases could be considered incomplete forms of bilateral clefts of the lip.

Keywords

oral clefts; subphenotype; dental anomalies; agenesis; cleft palate; cleft lip

INTRODUCTION

In 1942, Fogh-Andersen provided evidence that cleft lip and cleft palate, which frequently occur together, are developmentally distinct entities. However, differences in the etiology or epidemiology of these complex traits may remain undetected, because of the high variability in disease phenotype. While many studies assign cleft phenotype as simply ‘affected’ or ‘unaffected’ status, evidence indicates that these phenotypes are sometimes overlooked and should be fully considered relative to other clinical markers that may help unravel the genetic basis for the condition (Rice *et al.*, 2001).

The development of tooth germs and the occurrence of cleft lip/palate have a close embryological relationship in terms of timing and anatomical position, and numerous studies have reported the presence of dental anomalies in association with various forms of cleft lip, cleft palate, or both (Jordan *et al.*, 1966; Ranta, 1982, 1983, 1986; Werner and Harris, 1989; Tsai *et al.*, 1998; Shapira *et al.*, 2000; Slayton *et al.*, 2003). It has been proposed that individuals with clefts present considerably more dental anomalies than do individuals without clefts, and, moreover, that severity of anomalies appears to be directly related to severity of the cleft

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(Adams and Niswander, 1967; Schroeder and Green, 1975; van den Boogaard *et al.*, 2000; Eerens *et al.*, 2001; Slayton *et al.*, 2003; Vieira, 2003; Aizenbud *et al.*, 2005; Stahl *et al.*, 2006). Recent studies have implied that the presence of dental anomalies may represent an additional clinical marker for oral clefts, suggesting a common genetic background between the conditions. Furthermore, the hypothesis of broadening the cleft phenotype would allow for the identification of healthy individuals presenting an increased risk of carrying genes involved in cleft formation, and hence gene-mapping efforts will have increased power and the ability to provide effective genetic counseling (reviewed by Weinberg *et al.*, 2006).

The purpose of this study was to determine if cleft phenotypes and associated dental anomalies could be used in combination to provide new definitions of cleft subphenotypes.

MATERIALS & METHODS

Participants

The cleft group consisted of 500 individuals aged 4-59 years (average age, 17.3 yrs) receiving treatment at the Hospital of Rehabilitation and Craniofacial Anomalies of the University of São Paulo, Bauru, Brazil, with no history of syndromic clefting. Control individuals consisted of 500 healthy, non-related people, aged 4-94 years (average age, 36.8 yrs), the great majority of whom were patients and students at Bauru Dental School. The study was conducted with the consent of the participants and approval of the Research and Ethics Committee of the aforementioned institution. In the case of children under 15 years of age, consent was also requested from their parents or from the individual legally in charge of the child.

Determination of Cleft Phenotypes

Individuals with clefts were examined clinically and through their medical records so that we could determine the cleft type and side to describe each individual's cleft status. Cleft status was based on cleft completeness (comprised of primary and secondary palates entirely) or incompleteness, and on laterality (left, right, bilateral, and central in the cases of median clefts and cleft palate only). An “unknown” cleft status indicated that either cleft type or side could not be determined, even after medical records were reviewed.

Determination of Dental Anomalies

Dental anomalies such as tooth agenesis (including hypodontia and oligodontia), microdontia, supernumerary teeth, tooth malposition (rotation or inclination), impaction, shape anomalies, and transposition were assessed clinically and through radiographs and were recorded for each individual. For every anomaly, the inclusion criterion was that at least 1 permanent tooth was affected (children 8 yrs old or younger were excluded, mainly because sometimes premolar tooth buds are not visible at younger ages). Instances of anomalies adjacent to the cleft area (affecting maxillary central incisors, lateral incisors, or canines) were not included, because the absence of such teeth was likely the consequence of developmental anomalies at the cleft site. Multiple anomalies were characterized by the simultaneous presence of 2 or more types of dental anomalies in the same individual.

Statistical Analysis

Chi-square and Fisher's exact probabilities were evaluated on all sets of comparisons. Differences observed in the frequencies of dental anomalies between cleft and control groups were assessed by the Chi-square test with statistical significance set at $p \leq 0.05$. Odds ratio calculations were also performed. Regarding differences in the frequencies of dental anomalies between different cleft subphenotypes and control individuals, significance figures were accounted for by the Bonferroni correction, based on the number of tests carried out. With the

Bonferroni correction, alpha will be 0.0002 (0.05/176 comparisons). Median and unknown-type clefts were not included in the analysis (Table 1).

RESULTS

Cleft Phenotypes

Of the 500 individuals with clefting, 400 had a cleft lip with cleft palate (168 with left cleft lip, 154 with bilateral cleft lip, 76 with right cleft lip, and two with median clefts), six had cleft lip only (two on the right side and four on the left side), 66 had cleft palate only, and 28 had unknown cleft types.

These cleft types were further subdivided based on cleft completeness or incompleteness and laterality, which generated 18 subtypes of cleft, with each individual's cleft status thoroughly described (Table 1). Since only six individuals had cleft lip only (unilateral left, n = 4; unilateral right, n = 2), we decided to include them in the cleft lip and palate group for statistical analysis. The exclusion of the ‘cleft lip only’ group did not substantially change the results (data not shown).

Dental Anomalies

Significant differences were observed for the frequencies of dental anomalies between individuals of each cleft status and control individuals (Table 1). Cleft individuals presented significantly more dental anomalies than did control individuals ($p = 0.00001$). Tooth agenesis ($p = 0.00001$), microdontia ($p = 0.006$), malposition ($p = 0.00001$), transposition ($p = 0.0011$), supernumerary teeth ($p = 0.00001$), and multiple anomalies ($p = 0.00001$) were consistently more frequent in the cleft group. Tooth impaction also tended to be more common in the cleft group ($p = 0.05$) (Table 2).

Regarding tooth agenesis, excluding third molars [which were the teeth most frequently absent in both persons with clefting (179/352; $p = 0.00001$) and control individuals (34/62; $p = 0.00001$)], premolars were most commonly absent in the cleft group (108/352; $p = 0.0002$), with no significant differences regarding each individual's cleft status, while control individuals presented more agenesis of the lateral incisors (13/62; $p = 0.05$).

Additional data regarding frequencies of dental anomalies in both persons with clefting and control individuals are available in the online APPENDIX.

Searching for Cleft Subphenotypes

The frequency of tooth agenesis, microdontia, supernumerary teeth, and malposition was compared among persons with clefting, based on cleft and anomaly sides (Table 3). We observed that tooth agenesis occurred most frequently in those with complete cleft lip and palate, unilaterally or bilaterally, and also in those with incomplete bilateral cleft lip and palate plus cleft palate, when compared with control individuals (Table 1). Agenesis on the right side was more frequent with unilateral left clefts ($p = 0.01$), and agenesis on the left side was more frequent with unilateral right clefts ($p = 0.01$) (Table 3). The absence of maxillary left lateral incisors was significantly associated with unilateral right clefts (12/78; $p = 0.007$). In contrast, right lateral incisors were most commonly absent with unilateral left clefts (15/172; $p = 0.00001$).

Following a similar pattern, microdontia and supernumerary teeth were also most frequent on the non-cleft side, particularly on the right side in those with unilateral left clefts ($p = 0.07$ and $p = 0.02$, respectively) (Table 3). However, microdontia did not seem to be associated with

any cleft phenotype, whereas the presence of supernumerary teeth was most frequently associated with complete unilateral cleft lip and palate (Table 1).

Malposition was also a common feature in cleft individuals, and showed preferential association with several cleft lip and palate phenotypes (Table 1). Mandibular canines were the most commonly affected teeth (39/47; $p = 0.00001$), often associated with complete bilateral cleft lip and palate.

Tooth impaction showed preferential association with complete cleft palate ($p = 0.00001$) (Table 1).

Transposition was observed in persons with complete bilateral or incomplete unilateral left cleft lip and palate, and affected mostly the maxillary premolars (6/7; $p = 0.007$), while no control individuals were affected.

The presence of multiple anomalies occurred most commonly in persons with complete and incomplete unilateral left cleft lip and palate (Table 1). Of the 23 persons with multiple anomalies, 20 included tooth agenesis. The most frequent combinations were agenesis plus malposition (11/20) and agenesis plus supernumerary teeth (8/20). Tooth agenesis plus microdontia was seen in one person only, with complete unilateral right cleft lip and palate.

Twelve additional cleft subphenotypes are proposed, based on the associated dental anomalies (Table 4).

DISCUSSION

Despite several reports on the incidence of dental anomalies in individuals with clefting, to our knowledge, no attempts have been made to use dental anomalies to subphenotype the three major categories of oral clefts (cleft lip only, cleft lip with cleft palate, and cleft palate only).

We used dental development to classify cleft types, with the goal of identifying subgroups that could have specific genetic contributions. Therefore, in addition to the major categories mentioned above, we have included detailed descriptions of the subphenotypes observed, which further enabled us to notice preferential associations of specific dental anomalies with each cleft subphenotype. We believe that these more sophisticated clinical definitions may be used as an additional tool in gene identification for clefts.

The use of medical records is a common practice in many studies. A drawback of this methodology is that when samples are collected from different sources, the reliability of the records is subject to the interpretation of the professional in charge of relating the examination or procedure. The medical records used in this study—from the Hospital of Rehabilitation and Craniofacial Anomalies (source of individuals with clefting) and Bauru Dental School (source of control individuals), both part of the University of São Paulo—were completed according to standardized nomenclature of the clinical descriptions, therefore minimizing the risk of misinterpretation of the findings. In addition, the same operator (AL) examined every individual clinically and assessed the individual's medical files, which also minimized errors due to misinterpretation of clinical descriptions. Nevertheless, although the records at the Hospital of Rehabilitation and Craniofacial Anomalies are very accurate and complete, consisting of all entries for previous and actual medical, psychological, nutritional and dental procedures, it was not possible to obtain information about cleft status for 28 persons. These patients were newly registered in the Hospital and had started their treatment in the Dental Clinics and had not yet been evaluated by the medical department. They were included in the study because their records had information on dental anomalies.

In agreement with previous reports, the individuals with clefts evaluated here presented considerably more dental anomalies than did control individuals, suggesting a common genetic background for these developmental processes (Shprintzen *et al.*, 1985; Ranta, 1986; Shapira *et al.*, 1999; Eerens *et al.*, 2001; Vieira, 2003). Previous reports have related higher frequencies of dental anomalies as the severity of the cleft increased (Adams and Niswander, 1967; van den Boogaard *et al.*, 2000; Eerens *et al.*, 2001; Slayton *et al.*, 2003; Aizenbud *et al.*, 2005). We found this to be true, since most cases of multiple anomalies affected individuals in the cleft lip and palate group. However, if this observation were *always* to be true, we would expect to see more anomalies in persons with bilateral cleft lip and palate; instead, we observed most cases of multiple anomalies to occur in individuals with unilateral left cleft lip and palate. We are unaware of studies with which to compare our results.

The frequency of tooth agenesis was significantly different between the groups in this study, observed in approximately 26% of persons with clefts and 7% of the control individuals. In humans, tooth agenesis is the most frequent congenital anomaly. Excluding the third molars, which are absent in approximately 20% of the general population, the prevalence of tooth agenesis varies from 2.6% to 11.3% (Nieminen *et al.*, 1995; Larmour *et al.*, 2005), and our results for the control group fell in that range. In cleft individuals, however, previous studies have reported a much higher incidence of tooth agenesis, as high as 67% to 77% (Shapira *et al.*, 2000; Aizenbud *et al.*, 2005). Discrepancies among results might be attributed to the inappropriate inclusion of missing teeth in the cleft area in those studies. The absence of such teeth is likely the consequence of local developmental anomalies at the cleft site and therefore was not considered in our study. Nevertheless, similar to our findings, hypodontia outside the cleft region was reported to occur in 27% of the affected children and 11% of their siblings, compared with only 3.6% of children without clefts (Eerens *et al.*, 2001).

Our results demonstrate that the prevalence of dental anomalies as a sign of disturbances in dental development was several times higher in individuals with clefts than in control individuals, and further indicate that dental anomalies can be considered an extended phenotype for clefts. We noticed that the presence of multiple anomalies was significantly more common with complete clefts, in particular, with unilateral left cleft lip and palate. We were also able to observe interesting patterns regarding the presence of some dental anomalies with specific cleft subphenotypes. For instance, although tooth agenesis was frequently observed in persons with both complete and incomplete cleft lip and palate, we noticed that it was significantly more frequent in unilateral complete cases, and both bilateral complete and incomplete plus cleft palate. Interestingly, supernumerary teeth were associated with unilateral complete and bilateral incomplete clefts. The observation of tooth malposition, with mandibular canines being the most affected teeth often associated with complete bilateral cleft lip and palate, is noteworthy and has not yet been described.

The consistent presence of dental anomalies on the opposite side of unilateral clefts, with preferential agenesis of the lateral incisor, leads us to believe that these specific unilateral clefts could be “unsuccessful” bilateral clefts, and should be considered carefully regarding the genetic etiology of different cleft types. We may hypothesize that the genes that contribute to laterality of the cleft may be different, resulting in alternate phenotypes for dental anomalies also. Although it seems unlikely that a single gene may be affecting both tooth and palate development, the simultaneous presence of oral clefts and dental anomalies, as has been overwhelmingly reported to occur, strongly indicates that a common genetic background is involved, and that single gene contributions cannot be discounted. Hence, we are proposing new subphenotypes based on dental development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Distribution of Individuals According to Cleft Status and Frequencies of Observed Dental Anomalies[a,b]

Cleft Type/ Subphenotype	No. Individuals	Agenesis	Microdontia	Supernumerary Teeth	Malposition	Impaction	Shape Anomaly	Transposition	Multiple Anomalies	Total Anomalies
Cleft palate										
Complete	21	4	0	0	0	**2**	0	0	**2**	**8**
	45	10	0	1	**4**	0	1	0	0	**16**
Incomplete + submucous										
Total	66	**14**	0	1	**4**	2	1	0	2	**24**
Cleft lip and palate										
Complete	300	**90**	7	**16**	**30**	3	0	5	**17**	**168**
Incomplete	104	**23**	1	**4**	**12**	1	0	2	3	**46**
Unilateral	250	**71**	6	**16**	**27**	3	0	3	**16**	**142**
Complete	175	**57**	5	**14**	**19**	2	0	1	**13**	**111**
Incomplete	75	14	1	2	**8**	1	0	2	**3**	**31**
Right	78	**28**	2	3	**9**	1	0	0	2	**45**
Complete	54	**23**	2	**3**	**6**	0	0	0	2	**36**
Incomplete	16	3	0	0	**3**	0	0	0	0	**6**
Incomplete + cleft palate	8	1	0	0	1	0	0	0	0	2
Left	172	**43**	4	**13**	**18**	2	0	3	**14**	**97**
Complete	121	**34**	3	**11**	**13**	2	0	1	**11**	**75**
Incomplete	46	9	1	**2**	**5**	0	0	**2**	3	**22**
Incomplete + cleft palate	5	0	0	0	0	0	0	0	0	0
Bilateral	154	**42**	2	**4**	**15**	1	0	4	**4**	**72**
Complete	125	**33**	2	2	**11**	1	0	**4**	4	**57**
Incomplete	8	1	0	**1**	**1**	0	0	0	0	3
Incomplete + cleft palate	17	**7**	0	**1**	**3**	0	0	0	0	**11**
Incomplete mixed	4	1	0	0	0	0	0	0	0	1
Right cleft lip + left cleft lip and palate	3	1	0	0	0	0	0	0	0	1
Left cleft lip + bilateral cleft palate	1	0	0	0	0	0	0	0	0	0
Median cleft	2	0	0	0	0	0	0	0	0	0
Total	406	**113**	8	**20**	**42**	4	0	7	**20**	**214**
Unknown type/side of cleft	28	4	1	1	1	0	1	0	1	9
Total clefts	500	**131**	**9**	**22**	**47**	6	2	7	**23**	**247**
No cleft (controls)	500	36	1	1	2	1	0	0	1	42

[a] Comparisons between persons with and without clefting. Median and unknown-type clefts were not included in the comparisons.

[b] Bold indicates statistically significant differences between persons with and without clefting (α = 0.0002).

Table 2

Differences in Observed Frequencies of Dental Anomalies between Persons with and without Clefting

Dental Anomaly	Cleft (n = 500)	Control (n = 500)	p Value*	Odds Ratio (95% CI)**
Agenesis	131	36	0.00001	4.5 (3.1- 6.7)
Microdontia	9	1	0.006	9.1 (1.1- 72.4)
Supernumerary	22	1	0.00001	22.9 (3.1-171.0)
Malposition	47	2	0.00001	25.8 (6.2-106.9)
Impaction	6	1	0.05	6.1 (0.7- 50.5)
Malformation	2	0	0.08	——
Transposition	7	0	0.001	——
Multiple	23	1	0.00001	24.1 (3.2-178.8)
Total	247	42	0.00001	10.6 (7.4- 15.2)

* Chi-square, 1 degree of freedom; $p \leq 0.05$ indicates statistical difference.

** CI, confidence interval.

Table 3

Number of Dental Anomalies Observed in Individuals with Clefts, Divided by Side of Anomaly

Anomaly	Side	Cleft Side: Right (n = 78)	Left (n = 172)	Bilateral (n = 154)	Central (n = 66)	p Value*
Agenesis	Right	5	16	2	2	0.01
	Left	8	6	5	0	0.01
	Bilateral	13	18	34	12	0.04
	Unknown	2	3	1	0	0.3
Microdontia	Right	0	3	0	0	0.06
	Left	2	1	1	0	0.3
	Bilateral	0	0	1	0	0.4
	Unknown	0	0	0	0	——
Supernumerary	Right	0	4	0	0	0.02
	Left	2	3	0	1	0.1
	Bilateral	0	0	0	0	——
	Unknown	1	6	4	0	0.2
Malposition	Right	3	11	6	1	0.4
	Left	4	3	2	2	0.3
	Bilateral	2	2	6	0	0.1
	Unknown	0	2	1	1	0.6

*Chi-square, 3 degrees of freedom; $p \leq 0.05$ indicates statistical difference.

Table 4

List of Cleft Subphenotypes Used in Epidemiological/Genetic Studies and the Proposed Additional Subphenotypes Based on Dental Development

Cleft Subphenotypes Used in the Most Recent Genetic Studies[a]	Proposed Cleft Subphenotypes Based on Dental Development[b]
• All cleft types • Cleft lip with or without cleft palate (CL/P) (all lips) • Cleft lip only (CLO) • Cleft lip and palate (CLP) • Cleft lip and palate + cleft palate (all palates) • Cleft palate only (CPO)	• Cleft lip with or without cleft palate (CL/P) – unilateral right ♦ with/without tooth agenesis outside the cleft area – unilateral left ♦ with/without tooth agenesis outside the cleft area ♦ with/without microdontia or supernumerary teeth on the non-cleft side ♦ with/without multiple dental anomalies – bilateral ♦ with/without tooth agenesis outside the cleft area ♦ with/without supernumerary teeth ♦ with/without malposition of lower canines ♦ with/without multiple dental anomalies – unsuccessful bilateral (unilateral CL/P with agenesis of the lateral incisor on the non-cleft side) ♦ with/without multiple dental anomalies • Cleft palate only (CPO) – complete ♦ with/without tooth impaction ♦ with/without multiple dental anomalies – incomplete ♦ with/without tooth malposition

[a] Vieira *et al.*, 2003, 2005; Avila *et al.*, 2006; Warrington *et al.*, 2006.

[b] Small number of persons with cleft lip only (CLO) did not allow for analysis of this specific cleft subtype.